PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

RIGAUT, Kathleen, D.
Saul, Ewing, Remick & Saul, LLP
Centre Square West
1500 Market Street, 38th Floor
Philadelphia, PA 19102-2186
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)
18 July 2000 (18.07.00)

Applicant's or agent's file reference
UMDNJ - 9808

IMPORTANT NOTIFICATION

International application No.
PCT/US99/25477

International filing date (day/month/year)
29 October 1999 (29.10.99)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address
RIGAUT, Kathleen, D.
Dann, Dorfman, Herrell and Skillman
Suite 720
1601 Market Street
Philadelphia, PA 19103-2307
United States of America

State of Nationality:
State of Residence:
Telephone No.: (215) 563-4100
Facsimile No.: (215) 563-4044
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
RIGAUT, Kathleen, D.
Saul, Ewing, Remick & Saul, LLP
Centre Square West
1500 Market Street, 38th Floor
Philadelphia, PA 19102-2186
United States of America

State of Nationality:
State of Residence:
Telephone No.: 215 972 8386
Facsimile No.: 215 972 2292
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☒ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
Eugénia Santos
Telephone No.: (41-22) 338.83.38

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C12N 15/85, 15/86, 15/11 | A1

(11) International Publication Number: **WO 00/26393**

(43) International Publication Date: 11 May 2000 (11.05.00)

(21) International Application Number: PCT/US99/25477

(22) International Filing Date: 29 October 1999 (29.10.99)

(30) Priority Data:
60/106,533 31 October 1998 (31.10.98) US

(71) Applicant *(for all designated States except US)*: UNIVERSITY OF MEDICINE AND DENTISTRY OF NEW JERSEY [US/US]; 30 Bergen Street, Newark, NJ 07107 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: RON, Yacov [US/US]; 24 Yorktown Road, East Brunswick, NJ 08816 (US). DOUGHERTY, Joseph, P. [US/US]; 18 Wolf's Farm, Hampton, NJ 08827 (US). CHEN, Chiann–Chyi [–/US]; 49 Marvin Lane, Piscataway, NJ 08854 (US).

(74) Agents: RIGAUT, Kathleen, D. et al.; Dann, Dorfman, Herrell and Skillman, Suite 720, 1601 Market Street, Philadelphia, PA 19103–2307 (US).

(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: A MYELOID PRECURSOR CELL USEFUL FOR GENE THERAPY AND FOR MODULATION OF IMMUNE RESPONSES

(57) Abstract

A long–lived, myeloid–committed stem cell population is disclosed. Also disclosed are methods and compositions for targeting this population with retrovirus vectors in gene therapy protocols for correcting congenital disorders of myeloid system and for potentiating immune responses to defined tumor and viral antigens.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/25477

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) : C12N 15/85, 15/86, 15/11
US CL : 435/325; 536/23.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/325; 536/23.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN, Medline, WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEN et al. Long-Term Contribution to the Myeloid Compartment by Lineage-Committed Stem Cells. Blood. 01 November 1998, Vol. 92, No. 9, pages 3210-3217, entire document.	1-19
Y	HUMEAU et al. Successful Reconstitution of Human Hematopoiesis in the SCID-hu Mouse by Genetically Modified, Highly Enriched Progenitors Isolated From Fetal Liver. Blood. 01 November 1997, Vol. 90, No. 9 pages 3496-3506, figure 2 and figure 5.	1-3
Y	PERSONS et al. Retroviral-Mediated Transfer of the Green Fluorescent Protein Gene Into Murine Hematopoietic Cells Facilitates Scoring and Selection of Transduced Progenitors In Vitro nd Identification of Genetically Modified Cells in Vivo. Blood. 01 September 1997, Vol. 90, No. 5, pages 1777-1786, figure 1.	6-7
X	US 5,502,176 A (TENEN et al.) 26 March 1996, entire document.	3-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 11 JANUARY 2000	Date of mailing of the international search report 08 FEB 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JOSEPH T. WOITACH Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

5

PATENT COOPERATION TREATY

PCT

REC'D 09 MAR 2001
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference UMDNT-98-08	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/25477	International filing date *(day/month/year)* 29 OCTOBER 1999	Priority date *(day/month/year)* 31 OCTOBER 1998
International Patent Classification (IPC) or national classification and IPC IPC(7): C12N 15/85, 15/86; C12N 15/11 and US Cl.: 435/325; 536/23.1		
Applicant UNIVERSITY OF MEDICINE AND DENTISTRY OF NEW JERSEY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22 MAY 2000	20 FEBRUARY 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer JOSEPH T. WOITACH
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet) (July 1998)★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/25477

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-35, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the claims:
pages 36-38, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the drawings:
pages 1-6, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE
[X] the claims, Nos. NONE
[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/25477

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	**Claims**	NONE	**YES**
	Claims	1-19	**NO**
Inventive Step (IS)	**Claims**	NONE	**YES**
	Claims	1-19	**NO**
Industrial Applicability (IA)	**Claims**	1-19	**YES**
	Claims	NONE	**NO**

2. citations and explanations (Rule 70.7)

Claims 1-19 lack novelty under PCT Article 33(2) as being anticipated by Chen et al. and Tenen et al.

Claims 1-19 encompass a composition of transduced myeloid-committed stem cells and methods of using the composition to express an exogenous genes under the regulation of a myeloid specific promoter in a subject. Several general groups of transgenes are recited in the claims 2, 5, 17 and 19, with specific transgenes associated with diseases/disorders that have defined genetic defects in claims 10-14. The specification describes methodology on how one would isolate the composition of cells and transduce them with retroviral constructs, and general methodology on how one would create the retroviral vectors with the specific transgene and general methodology on how one would treat a subject with a known genetic defect. No details on specific expression levels needed for successful treatment of a specific disease/disorder are discussed. One example of transducing cells with a retroviral vector is given and one prophetic example on how one could potentiate an immune response is described.

Chen et al. describe the isolation of myeloid-committed stem cells (entire document, in particular summarized in abstract and illustrated in figure 3). Further, they demonstrate the retroviral transduction and myeloid specific expression of a transgene in these cells. Finally, Chen et al. propose the use of these cells and other transgenes for the exogenous expression for therapy based treatment of genetic disorders and to potentiate an immune response (page 3216; last paragraph). While Chen et al. do not recite the general list of transgenes or specific transgenes associated with specific disorders/diseases, one of ordinary skill in the art would know how to use and practice the invention as claimed in light of Chen et al., as the transgenes listed in the claims represent genes that one would generally want to express. Therefor, Chen et al. anticipate the claimed invention.

Tenen et al. describe the isolation of the CD11B myeloid specific promoter and methods of using the promoter in vector systems to achieve myeloid specific expression of transgenes in (Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
myeloid cells. As reasoned above for Chen et al., one of ordinary skill in the art would know to use the genes recited in the claims in the expression vectors and methods described in Tenen et al. Therefor, Tenen et al. anticipate the claimed invention.

Persons et al. has been cited to demonstrate another source of a retroviral vector which could be substituted for the one described in Chen et al. or Tenen et al. for use in the methods of cell transduction. Humeau et al. has been cited as alternative source for myeloid progenitor cells. While the specification of the present application teaches methods to isolate a myeloid committed stem cell, claim 1 as written encompasses any composition comprising the myeloid stem cell. Therefor, bone marrow, a source of the myeloid progenitor stem cell, transduced as described by Humeau et al. anticipates claim 1. The general methodology described in the specification of the present application is prophetic and not reduced to practice, and so the prophetic use proposed by Humeau et al. for gene therapy (page 3504; last line) in light of the general reasoning discussed above for one skilled in the art, anticipate claims 2-19.

---------- NEW CITATIONS ----------
NONE